EFFECT OF ENDOTOXIN ON MYOCARDIAL PERFORMANCE

Lerner B. Hinshaw, et al

Oklahoma University

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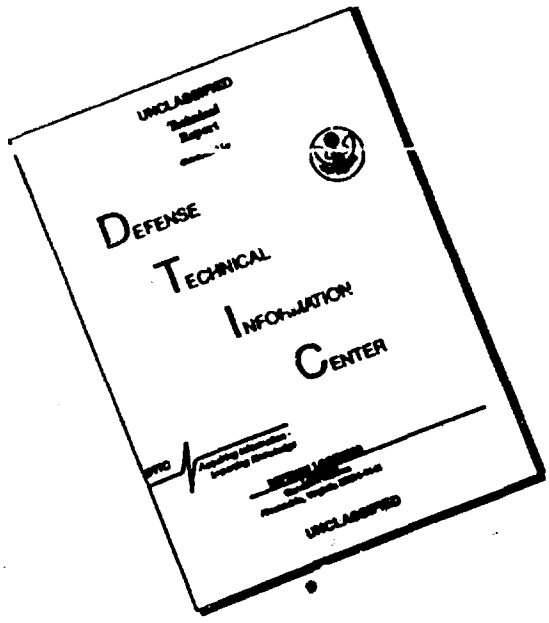

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Lerner B. Hinshaw, L. T. Archer, L. J. Greenfield, J. A. Miller, C. A. Guenter

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13. ABSTRACT

The effect of endotoxin on the heart is obscure, and results have been controversial. The purpose of the present study was to determine if there is a direct detrimental action of endotoxin on cardiac tissue. An isolated heart and ventilated lungs removed from a donor dog were perfused with venous blood from an intact heparinized animal. Pulmonary blood flow, aortic pressure, respiration, and blood temperature were maintained constant in the isolated preparation. Cardiac output was directly measured from aortic and coronary venous outflows. Left ventricular myocardial contractile force, intraventricular and aortic pressures, and oxygen uptake were determined. An LD_{90} injection of E. coli endotoxin was intravenously administered to the dog. Results indicate that endotoxin has no early detrimental effect on myocardial performance. Oxygen uptake and left ventricular contractile force were maintained at pre-endotoxin values or increased above control in the presence of severe systemic hypotension in the dog. Left ventricular end diastolic pressure was not elevated in any experiment, but ordinarily decreased after endotoxin. Coronary blood flow progressively increased, and vascular resistance significantly fell. While there was no evidence to support an early direct toxic action of endotoxin on myocardial tissue, results do not exclude the possibility of later indirect factors ultimately depressing myocardial integrity.

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Technical Report No. 73
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OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
800 Northeast Thirteenth Street
Oklahoma City, Oklahoma 73104

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EFFECT OF ENDOTOXIN ON MYOCARDIAL PERFORMANCE

It is generally agreed that the heart will ultimately fail in endotoxin shock; however, its contributory role in the development of the irreversible state is not clear. It has been demonstrated that venous return sharply decreases early after endotoxin due to intravascular pooling (10-12,26). It seems well established, therefore, that systemic hypotension is in large part promoted by peripheral, rather than direct, cardiac mechanisms.

Weil et al. (26) found no evidence for myocardial failure in the early phase of endotoxin shock, largely on the basis of normal electrocardiographic tracings. Others have found that large doses of endotoxin exert no perceptible detrimental effects on the myocardial extraction of oxygen or the coronary vasculature (18). It has been suggested that the heart is affected only indirectly by endotoxin because of unfavorable circulatory conditions (2). On the other hand, Solis and Downing (24) and Kadowitz and Yard (14) demonstrated cardiac depression early after endotoxin. In each instance, ventricular contractile force was diminished, and in the studies by Solis and Downing, contractile force was depressed even when arterial pressure was maintained.

The purpose of the following study was to determine if the heart is directly damaged by lethal injections of endotoxin under conditions in which respiratory and hemodynamic parameters were maintained constant. It was hoped that the studies would provide insight into the role of the heart in the development of systemic hypotension.

MATERIALS AND METHODS

The experimental procedure provided for the support of an isolated denervated left ventricle by the exchange of blood from a heparinized support animal. All experiments were conducted on adult mongrel dogs intravenously anesthetized with sodium pentobarbital, 30 mg/kg. The donor heart dog (average weight, 8.4 kg) was anesthetized, and the chest was opened along the midsternum region after the animal was placed on a constant volume respirator. The azygous vein and subclavian artery were ligated and sectioned between ties. Ligatures were loosely placed around the thoracic aorta distal to the subclavian artery, the brachiocephalic artery, and superior and inferior venae cavae. The pericardial sac was opened along its ventral surface and the animal was heparinized (3-5 mg/kg). The bagi were then cut in the neck region and the brachiocephalic artery was cannulated with a plastic tubing which extended to a height of 100 to 125 cm above the heart level. The superior vena cava was cannulated with a blood-filled plastic tubing led through a roller-type blood pump drawing blood from the inferior vena cava of the support dog. The tip of this tubing lay in the central vein of the animal proximal to the hepatic vein orifice. To prepare the donor heart for transfer to the perfusion system without interruption of blood flow, the brachiocephalic outflow from the heart was opened, allowing blood to fill the tubing exerting a hydrostatic pressure providing adequate coronary perfusion (pressure > 80 mm Hg). The aorta was then tied distal to the brachiocephalic artery, the superior vena caval inflow from the pump was commenced at 120 ml/min, and the inferior vena cava was immediately ligated. Bllod from the aortic outflow was collected in a plastic reservoir and returned to the intact

support dog at a flow rate equal to the superior vena caval inflow. The heart and lungs were then removed from the chest and transferred to the external system, with adequate coronary pressure and flow constantly provided. Support animals were approximately three times heavier than heart donor animals in order to minimize the stress of prolonged perfusion in the intact animal.

A strain gauge arch was sutured to the lateral wall of the left ventricle for measurement of myocardial contractile force (3). Left ventricular pressure was measured by insertion of a short, large-bore plastic drainage tubing into the right ventricle via the atrium and cannulating the pulmonary artery from a T connection previously secured to the superior vena caval inflow tubing. The cannulation of the pulmonary artery required only a few seconds, during which time the coronary vessels were retrograd-perfused with blood by hydrostatic pressure from the aortic outflow tubing. Coronary venoust blood was collected from the right ventricular drainage tubing into a plastic reservoir, and together with brachiocephalic outflow returned to the dog via a second pump. Cardiac output was taken as the sum of aortic outflow and coronary flow, both measured with a cylinder and stop watch. Temperature of coronary venous blood was monitored with a temperature probe. Aortic pressure, left ventricular pressure, cardiac contractility of the isolated heart, and the mean systemic pressure of the support dog were continuously monitored on a Sanborn recorder. Left ventricular pressure was alternately recorded by means of a Statham pressure transducer, on a sensitive (0-40 mm Hg) range and a scale (0-200) registering both systolic and diastolic pressures.

Mean aortic pressure and cardiac output were steadily increased in the isolated heart preparation by adjustment of a screw clamp on the aortic outflow and elevation of pump speed supplying the pulmonary artery. The lungs of the isolated heart preparation were continuously ventilated by a Starling constant volume respirator. Coronary arterial and venous Po_2, Pco_2, and pH were followed by utilizing an Instrumentation Laboratories blood gas analyzer. Oxygen content of coronary arterial and venous blood was measured by a Natelson Microgasometer. Simultaneously obtained coronary flow measurements permitted the calculation of oxygen uptake by multiplying the A-V O_2 difference by coronary flow.

During an equilibration period, aortic pressures were stabilized at approximately 125 to 130 mm Hg and cardiac output at 50 ml/min/kg body wt based on the weight of the heart donor dog. These pressure and flow values supported and maintained left ventricular systolic and diastolic pressures, coronary flow, coronary blood temperature, and oxygen uptake in the physiological range, and were therefore maintained constant during the course of the experiments (180 min). Following the equilibration period, when all values of the various parameters achieved a relative constancy, a 30-min control period was run coli endotoxin (Difco, Detroit), 1.5 mg/kg. Endotoxin was administered intravenously in the support animal, and in some experiments was additionally injected into the pulmonary arterial inflow of the isolated heart. Experiments were concluded at the death of the dogs or not later than 180 min postendotoxin.

Stroke work (19) in gram·meters was calculated from the formula:

$$(MAP-LVEDP)\ (SV)\ (1.36)/100$$

where MAP = mean aortic pressure (mm Hg); LVEDP = left ventricular and

diastolic pressure (mm Hg); and SV = stroke volume in ml, determined by dividing cardiac output by heart rate. The acceleration component of ventricular stroke work was disregarded in the calculations on the basis that it represents less than 1% of total stroke work (20). Cardiac power was determined by the expression of work per second.

Maximum change in left ventricular pressure (dP/dT) occurring during isometric contraction of the left ventricle (19,21) was determined from analysis of the slope of a line drawn tangentially to the steepest portion of the ventricular tracing and expressed in mm Hg/sec.

RESULTS

Table I illustrates the effect of an LD_{90} intravenous injection of endotoxin in the intact support dogs supplying blood to the isolated heart. Mean systemic pressure fell sharply and remained low during the postendotoxin period, while heart rate was insignificantly altered.

Several parameters were maintained constant in the perfused heart-lung preparation. These are shown in Table II. Mean aortic pressure, cardiac output, blood temperature, and respiration rate and depth were all maintained relatively constant in each experiment. It is noted that although systemic pressure of the support dog fell to severly low values after endotoxin injection, coronary perfusion pressure of the isolated heart was maintained in the normal range. These values were deliberately maintained constant because of their direct influences on various work performance and metabolic characteristics of the heart (4,21).

Table III demonstrates the effect of endotoxin on the hemodynamics and metabolism of the isolated heart. All individual heart preparations

showed considerable coronary hemodynamic alterations, with increasing coronary flow and decreasing coronary vascular resistance. Mean coronary flow increased nearly 60% above control, while resistance fell to approximately half the initial values within 2 hr after endotoxin. Data in Table III that oxygen uptake of the left ventricle varied insignificantly during the control and shock stages. There were no regular changes in heart rate, although no experiment demonstrated bradycardia after endotoxin.

It was decided to evaluate the effects of endotoxin on certain cardiac performance parameters. Table IV describes the results. Left ventricular contractile force did not decrease in any experiment, but ordinarily increased. Because of individual variation, however, mean values were statistically unaltered by endotoxin. Left ventricular end diastolic pressure (LVEDP) usually decreased in individual hearts following endotoxin injection. On the average, all values tended to decrease 2 to 3 hr after endotoxin. The maximum rate of change in pressure (dP/dT) increased furing the postendotoxin period. Stroke work (gram·meters) was relatively unaffected, although there was a tendency for a decrease, presumably on the basis of a slight elevation of heart rate in individual experiments. On the other hand, when cardiac power (work/sec) was calculated, a high degree of constancy was seen during both the control and shock periods.

Table V summarizes pH, Po_2, and Po_2 alterations in coronary arterial and venous blood. There was a significant decrease in pH by 30 to 90 min after endotoxin ($p \leq 0.05$). Pco_2 values remained relatively constant, and although Po_2 fell in coronary artery blood and rose in coronary venous blood, changes are statistically insignificant because of individual

variation.

DISCUSSION

The over-all objective of this study was to determine the role of the heart in contributing to the precipitation of irreversible endotoxin shock. Experiments were principally designed to determine if the heart was directly damaged by endotoxin when hemodynamic and respiratory parameters were controlled. In order to reveal possible direct toxic actions of endotoxin on the myocardium, aortic pressure, cardiac output, blood temperature, and respiratory rate and depth were maintained constant during a 2- to 3-hr postendotoxin observation period. Blood was continuously exchanged between an endotoxin-shocked animal and the isolated working heart-lung preparation. Results from these experiments failed to reveal a single instance of endotoxin toxicity on myocardial work performance or oxidative metabolism, even though the heart received blood from an animal which was severely hypotensive and acidotic. Coronary flow sharply increased and coronary vascular resistance devreased, while myocardial oxygen uptake remained relatively unchanged during the shock period. Left ventricular contractile force and dP/dT increased in all individual experiments after endotoxin administration, while stroke work and cardiac power remained relatively constant. Left ventricular end diastolic pressure did not increase in a single experiment after endotoxin injection, but ordinarily demonstrated a steady decrease. Results from the present study therefore offer no support for a direct toxic action of endotoxin on myocardial tissue. These findings support the conclusions

of some investigators (2,18,26), but are in disagreement with others (14,24).

Albert, Glass, and Carter (1) ascribed primary heart failure as the initiating deleterious factor in hemorrhagic shock, while Siegel and Downing (23) considered the heart to be damaged subsequently only to the prolonged systemic hypotension. It has also been observed that cardiac function is depressed only temporarily in hemorrhagic shock and ultimately recovers, even during the hypotensive state(5).

Lefer and others (15-17) have identified a myocardial depressor substance present in the plasma of animals in late hemorrhagic shock. They have postulated that this substance may play an important role in the pathogenesis of irreversibility by depressing excitation-contraction coupling or by impairing the cardiac contractile machinery directly. The present study provides no evidence for the release of a myocardial depressant factor in the plasma of the endotoxin-poisoned animal. It is conceivable that an inotropic adrenergic endogenous agent released after endotoxin could have masked the myocardial effects of a circulating myocardial depressant substance; however, recent studies utilizing beta adrenergic blockade before and after endotoxin have failed to reveal a depressant action of endotoxin on the myocardium (13).

The problem of the precise role of the heart in the developement of irreversible endotoxin shock is complicated by events occurring in the periphery which most assuredly influence cardiac output adversely (12,26), causing its decrease on the basis of a diminished venuous return. The resultant systemic hypotension may ultimately compromise cardiac integrity because of diminished coronary blood flow.

The present experiments appear to exclude a direct toxic overwhelming action of endotoxin on myocardial performance. Gilbert (8) pointed out that there was no evidence for a direct adverse effect of endotoxin on myocardial function. More recently Siegel, Greenspan, and Del Guercio (22), and Thal and Bell (25) have demonstrated myocardial failure in septic shock in patients, and a logical argument for a general cardiac theory of shock has been developed by Crowell and Guyton (6,7). Results from the present study suggest that primary cardiac endotoxin-induced toxicity is not a significant factor in the pathogenesis of early experimental septic shock, but do not exclude the possibility that the indirect effects of endotoxin may perform important roles in the eventual depression of cardiac integrity.

SUMMARY

The effect of endotoxin on the heart is obscure, and results have been controversial. The purpose of the present study was to determine if there is a direct detrimental action of endotoxin on cardiac tissue. An isolated heart and ventilated lungs removed from a donor dog were perfused with venous blood from an intact heparinized animal. Pulmonary blood flow, aortic pressure, respiration, and blood temperature were maintained constant in the isolated preparation. Cardiac output was directly measured from aortic and coronary venous outflows. Left ventricular myocardial contractile force, intraventricular and aortic pressures, and oxygen uptake were determined. An LD_{90} injection of E. coli endotoxin was intravenously administered to the dog. Results indicate that endotoxin has no early detrimental effect

on myocardial performance. Oxygen uptake and left ventricular contractile force were maintained at pre-endotoxin values or increased above control in the presence of severe systemic hypotension in the dog. Left ventricular end diastolic pressure was not elevated in any experiment, but ordinarily decreased after endotoxin. Coronary blood flow progressively increased, and vascular resistance significantly fell. While there was no evidence to support an early direct toxic action of endotoxin on myocardial tissue, results do not exclude the possibility of later indirect factors ultimately depressing myocardial integrity.

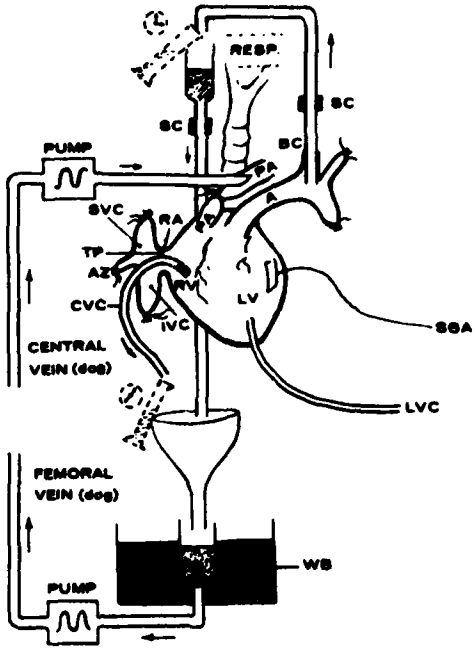

FIG. 1. Diagram of isolated perfused heart preparation. Blood is obtained from central vein of the dog (catheter tip within thorax) and subsequently returned to femoral vein.

PA = pulmonary artery
A = aorta
BC = brachiocephalic artery
RA = right atrium
RV = right ventricle
LV = left ventricle
AZ = azygous vein
SVC = superior vena cava
IVC = inferior vena cava
SC = adjustable screw clamp
resp = constant volume respirator
SGA = strain gauge arch
LVC = left ventricular catheter
CVC = coronary vein catheter
TP = temperature probe
WB = water bath at controlled temperature

TABLE I

Effect of Endotoxin (LD_{90}) on Intact Support Animal

(Mean ± SE; N = 7)

Period	Mean Systemic Arterial Pressure (mm Hg)	Heart Rate (min)
Control No. 1 (minus 30 min)	126 (± 4)	156 (± 7)
Control No. 2 (zero time)	127 (± 4)	144 (± 12)
Postendotoxin:		
30-90 min	52 (± 9)	155 (± 8)
90-150 min	48 (± 6)	162 (± 9)
150-180 min	54 (± 11)	173 (± 17)

TABLE III

Effect of Endotoxin (LD_{90}) on Hemodynamics and Metabolism of Isolated Heart Preparation

(Mean ± SE; N = 7)

Period	Coronary Flow (ml/min)	Coronary Vascular Resistance (mm Hg/ml/min)	Heart Rate (min)	Oxygen Uptake (ml/min/100 g left ventricle)
Control No. 1 (minus 30 min)	97 (± 16)	1.46 (± 0.13)	143 (± 8)	14.2 (± 2.1)
Control No. 2 (zero time)	95* (± 19)	1.54 (± 0.19)	144 (± 11)	11.7† (± 2.0)
Postendotoxin:				
30-90 min	142 (± 27)	0.96 (± 0.13)	163 (± 5)	17.1 (± 5.9)
90-150 min	159 (± 25)	0.79 (± 0.07)	157 (± 5)	12.5 (± 3)
150-180 min	160 (± 26)	0.76 (± 0.04)	151 (± 7)	13.5 (± 2.3)

* 191 (± 43) ml/min/100 g left ventricle.

* 137 (± 30) ml/min/100 g heart.

† 8.4 (± 1.4) ml/min/100 g heart.

TABLE II

Controlled Parameters in Isolated Heart Preparation* (Mean ± SE; N = 7)

Period	Mean Aortic Pressure (mm Hg)	Cardiac Output		Blood Temperature
		ml/min	ml/min/kg†	
Control No. 1 (minus 30 min)	129 (± 8)	405 (± 36)	51 (± 6)	35.9 (± 0.3)
Control No. 2 (zero time)	129 (± 8)	407 (± 37)	51 (± 6)	35.9 (± 0.4)
Postendotoxin:				
30-90 min	126 (± 9)	404 (± 40)	51 (± 6)	35.6 (± 0.3)
90-150 min	121 (± 9)	401 (± 44)	51 (± 7)	35.6 (± 0.5)
150-180 min	126 (± 10)	385 (± 66)	49 (± 9)	36.2 (± 0.5)

*Respiration rate and depth maintained constant in each experiment.

†Cardiac output value based on weight of dog supplying heart.

TABLE IV

Effect of Endotoxin on Cardiac Performance (Mean ± SE; N = 7)

Period	Left Ventricular Contractile Force (mm)*	LVEDP† (mm Hg)	dP/dT (mm Hg/sec)	Stroke Work (g·meter)	Power (Work/Sec)
Control No. 1 (minus 30 Min.)	21.4 (± 2.7)	+4.0 (± 0.8)	3501 (± 617)	5.1 (± 0.6)	11.9 (± 1.6)
Control No. 2 (zero time)	21.8 (± 1.9)	+2.7 (± 1.2)	2979 (± 497)	5.1 (± 0.8)	12.0 (± 1.6)
Postendotoxin:					
30-90 min	26.2 (± 4.3)	+0.4 (± 0.8)	5012 (± 1428)	4.4 (± 0.6)	11.8 (± 1.7)
90-150 min	30.4 (± 5.7)	-0.2 (± 1.1)	4416 (± 1192)	4.2 (± 0.7)	11.5 (± 1.9)
150-180 min	25.8 (± 2.8)	0 (± 1.5)	4198 (± 831)	4.8 (± 0.9)	12.2 (± 2.1)

*Measured by strain gauge arch.

†LVEDP = Left ventricular end diastolic pressure.

TABLE V

Effect of Endotoxin on pH and Blood Gas Tensions in Isolated Heart Preparation

(Mean ± SE; N = 7)

Period	pH*	Po_2	Pco_2
Control No. 1 (minus 30 min)	A 7.49 (± 0.03)	70 (± 8)	22 (± 2)
	V 7.46 (± 0.03)	24 (± 2)	28 (± 2)
Control No. 2 (zero time)	A 7.50 (± 0.04)	73 (± 8)	22 (± 2)
	V 7.46 (± 0.04)	24 (± 3)	28 (± 3)
Postendotoxin:			
30-90 min	A 7.37 (± 0.04)	64 (± 9)	22 (± 2)
	V 7.35 (± 0.04	29 (± 3)	27 (± 3)
90-150 min	A 7.31 (± 0.06)	55 (± 5)	25 (± 2)
	V 7.29 (± 0.06)	33 (± 2)	29 (± 2)
150-180 min	A 7.32 (± 0.10)	64 (± 8)	24 (± 2)
	V 7.31 (± 0.10)	36 (± 5)	29 (± 3)

*A = Coronary artery.

V = Coronary vein.

REFERENCES

1. Albert HM, Glass BA, Carter RL: The role of the heart in shock: exsanguination studies. Ann Surg 34:48-52, 1968.
2. Alican F, Dalton, ML Jr, Hardy JD: Experimental endotoxin shock. Am J Surg 103:702-708, 1962.
3. Boniface KJ, Brodie OJ, Walton RP: Resistance strain gauge arches for direct measurement of heart contractile force in animals. Proc Soc Exp Biol Med 84:263-266, 1953.
4. Braunwald E. Sarnoff SJ, Case RB, et al: Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary flow. Am J Physiol 192:157-163, 1958.
5. Bugg-Asperheim B, Kjekshus J: Left ventricular pressure and maximum rate of pressure rise as determinants of myocardial oxygen consumption during hemorrhagic hypotension in dogs. Acta Physiol Scand 78:174-183, 1970.
6. Crowell JW, Guyton AC: Evidence favoring a cardiac mechanism in irreversible hemorrhagic shock. Am J Physiol 201:893-896, 1961.
7. Crowell JW, Guyton AC: Further evidence favoring a cardiac mechanism in irreversible hemorrhagic shock. Am J Physiol 203:248-252, 1962.
8. Gilbert RP: Mechanisms of the hemodynamic effects of endotoxin. Physiol Rev 40:245-279, 1960.
9. Gleason WL, Braunwald E: Studies on the first derivative of the ventricular pressure pulse in man. J Clin Invest 41:80-91, 1962.

10. Hinshaw LB, Gilbert RP, Kuida H, et al: Peripheral resistance changes and blood pooling after endotoxin in eviscerated dogs. Am J Physiol 195:631-634, 1958.

11. Hinshaw LB, Emerson TE Jr, Reins DA: Cardiovascular responses of the primate in endotoxin shock. Am J Physiol 210:335-340, 1966.

12. Hinshaw LB, Shanbour LL, Greenfield LJ, et al: Mechanism of decreased venous return: subhuman primate administered endotoxin. Arch Surg 100:600-606, 1970.

13. Hinshaw LB, Greenfield LJ, Archer LT, et al: Effects of endotoxin on myocardial hemodynamics, performance and metabolism during beta adrenergic blockade. Proc Soc Exp Biol Med 137:1217-1224, 1971.

14. Kadowitz PJ, Yard AC: Circulatory effects of hydrocortisone and protection against endotoxin shock in cats. Europ J Pharm 9:311-318, 1970.

15. Lefer AM, Cowgill R, Marshall FF, et al: Characterization of a myocardial depressant factor present in hemorrhagic shock. Am J Physiol 213:492-498, 1967.

16. Lefer AM, Rovetto JJ: Influence of a myocardial depressant factor on physiologic properties of cardiac muscle. Proc Soc Exp Biol Med 134:269-273, 1970.

17. Lefer AM: Role of a myocardial depressant factor in the pathogenesis of circulatory shock. Fed Proc 29:1836-1847, 1970.

18. Londe SP, Massie H, Monafo WW Jr, et al: Resistance of the isolated canine heart to endotoxin. Surgery 61:466-470, 1967.

19. Ross J Jr, Sonnenblick EH, Kaiser GA, et al: Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli. Circ Res 16:332-342, 1965.

20. Sarnoff SJ, Berglund E: Ventricular function. I. Starlings law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 9:706-718, 1954.

21. Sarnoff SJ, Braunwald E. Welch GH Jr, et al: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 192:148-156, 1958.

22. Siegel JH, Greenspan M, Del Guercio LR: Abnormal vascular tone, defective oxygen transport and myocardial failure in human septic shock. Ann Surg 165:504-517, 1967.

23. Siegel HW, Downing SE: Reduction of left ventricular contractility during acute hemorrhagic shock. Am J Physiol 218:772-779, 1970.

24. Solis RT, Downing SE: Effects of E. coli endotoxemia on ventricular performance. Am J Physiol 211:307-313, 1966.

25. Thal A, Bell H: The peculiar hemodynamics of septic shock. Postgrad Med 48:106-114, 1970.

26. Weil MH, MacLean LD, Visscher MB, et al: Studies on the circulatory changes in the dog produced by endotoxin from Gram-negative microorganisms. J Clin Invest 35:1191-1198, 1956.